Is There Anything New About Preoxygenation? Duh, Yeah!

Peter D. Slinger, MD, FRCPC

How, and how long, should you preoxygenate your next patient before induction of anesthesia? This is a very difficult question. Respiratory physiology is complicated. If you think the answer is simple, you don't understand the question. However, you make this complex decision for each patient and you probably do it multiple times every working day. Among the many factors that go into this decision are the following: How rapidly is this particular patient going to desaturate if there is a delay establishing ventilation? Is there likely to be difficulty with ventilation and/or intubation? What is the safe level of desaturation in this specific patient?

The review article by Nimmagadda et al[1] in this issue of *Anesthesia & Analgesia* helps the clinician to make this potentially very important decision about preoxygenation. For the majority of patients, the authors suggest that 3 minutes of normal tidal breathing F_{IO_2} 1.0 with a fresh gas flow that exceeds the resting minute ventilation (approximately 5 L/min) is adequate and reliable. Longer periods and forced deep breathing are unlikely to add a clinically useful extra reserve of oxygen in the patient's lungs or blood.

The authors elaborate on 4 specific clinical populations: pregnant women need a higher fresh gas flow (10 L); obese patients benefit significantly from a head-up position; pediatric patients only need 2 minutes of preoxygenation; and elderly patients may require 5 minutes.

Nimmagadda et al finish the review by debunking several myths about the risks of preoxygenation: a diagnosis of accidental esophageal intubation is not more likely to be missed because of preoxygenation (does anyone actually believe this?); absorption atelectasis can be easily reversed by a routine recruitment maneuver at the start of ventilation; and there is no good evidence for the harmful effects of reactive oxygen species because of a transient high F_{IO_2}.

However, there are several potentially negative aspects of complete preoxygenation that the authors do not discuss: applying a tight-fitting face mask for 2 minutes to a 2-year-old is likely to be stressful for the patient, his or her parents, and the anesthesiologist; and in some dire emergencies, such as a prolapsed cord, the time for full preoxygenation may not be possible without undue risk to the patient(s). Also, I do not know the optimal method of preoxygenation for a patient who has received bleomycin (I use F_{IO_2} 0.4 if I do not anticipate a problem with intubation, but I cannot offer any science to back up my practice).

In the middle of the review article, in the section on technique, are (what I believe to be) the 2 key points:

1. We can simply and routinely monitor the adequacy of our preoxygenation. If the end-tidal O_2 concentration (E_{TO_2}) is ≥90%, the patient has been adequately preoxygenated. Induction can commence. Do you watch this number routinely? I confess I do not, but I plan to start, and I believe the next generation of anesthesiologists will monitor this faithfully.
2. In critical situations, we can improve our preoxygenation with the use of high-flow nasal oxygen. This is a very interesting technique that is starting to move into the operating room from the intensive care unit, where it has been introduced as noninvasive ventilatory support for infants and now for adults. Humidified oxygen flows of up to 50–70 L/min provide not only a high F_{IO_2} but also seem to decrease airway deadspace and to provide a level of continuous positive airway pressure CPAP (see Table).[2] This concept has been given the unfortunate name of transnasal humidified rapid insufflation ventilator exchange, and the acronym THRIVE[3] (which sounds like a geriatric dietary supplement). I think just calling it high-flow nasal O_2 would suffice. I believe we are going to soon see this device used for oxygenation and ventilation support before and after extubation in chronic obstructive pulmonary disease, sleep apnea, obese patients, and others at risk of desaturation. This device is already well known among the difficult airway subgroup of anesthesiologists. It may become a game changer.

Table. Proposed Benefits of High-Flow Nasal Oxygen[2]

Achieve a high and stable F_{IO_2}
Decreased upper airway anatomical deadspace
Decreased work of breathing
Warmed and humidified inspired gas
Continuous positive airway pressure (up to 8 cm H_2O)
Lung recruitment

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Preoxygenation: Physiologic Basis, Benefits, and Potential Risks

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Preoxygenation before anesthetic induction and tracheal intubation is a widely accepted maneuver, designed to increase the body oxygen stores and thereby delay the onset of arterial hemoglobin desaturation during apnea. Because difficulties with ventilation and intubation are unpredictable, the need for preoxygenation is desirable in all patients. During emergence from anesthesia, residual effects of anesthetics and inadequate reversal of neuromuscular blockade can lead to hypoventilation, hypoxemia, and loss of airway patency. In accordance, routine preoxygenation before the tracheal extubation has also been recommended. The objective of this article is to discuss the physiologic basis, clinical benefits, and potential concerns about the use of preoxygenation. The effectiveness of preoxygenation is assessed by its efficacy and efficiency. Indices of efficacy include increases in the fraction of alveolar oxygen, increases in arterial oxygen tension, and decreases in the fraction of alveolar nitrogen. End points of maximal preoxygenation (efficacy) are an end-tidal oxygen concentration of 90% or an end-tidal nitrogen concentration of 5%. Efficiency of preoxygenation is reflected in the rate of decline in oxyhemoglobin desaturation during apnea. All investigations have demonstrated that maximal preoxygenation markedly delays arterial hemoglobin desaturation during apnea. This advantage may be blunted in high-risk patients. Various maneuvers have been introduced to extend the effect of preoxygenation. These include elevation of the head, apneic diffusion oxygenation, continuous positive airway pressure (CPAP) and/or positive end-expiratory pressure (PEEP), bilevel positive airway pressure, and transnasal humidified rapid insufflation ventilatory exchange. The benefit of apneic diffusion oxygenation is dependent on achieving maximal preoxygenation, maintaining airway patency, and the existence of a high functional residual capacity to body weight ratio. Potential risks of preoxygenation include delayed detection of esophageal intubation, absorption atelectasis, production of reactive oxygen species, and undesirable hemodynamic effects. Because the duration of preoxygenation is short, the hemodynamic effects and the accumulation of reactive oxygen species are insufficient to negate its benefits. Absorption atelectasis is a consequence of preoxygenation. Two approaches have been proposed to reduce the absorption atelectasis during preoxygenation: a modest decrease in the fraction of inspired oxygen to 0.8, and the use of recruitment maneuvers, such as CPAP, PEEP, and/or a vital capacity maneuver (all of which are commonly performed during the administration of anesthesia). Although a slight decrease in the fraction of inspired oxygen reduces atelectasis, it does so at the expense of a reduction in the protection afforded during apnea. (Anesth Analg 2016;XXX:00–00)

The ability of preoxygenation, using a high fraction of inspired oxygen (F_{IO_2}) before anesthetic induction and tracheal intubation, to delay the onset of apnea-induced arterial oxyhemoglobin desaturation has been appreciated for many years.[1–3] For patients at risk for aspiration, during rapid sequence induction/intubation where manual ventilation is undesirable, preoxygenation has become an integral component.[4–7] Preoxygenation is also important, when difficulty with ventilation or tracheal intubation is anticipated and when the patient has limited oxygen (O_2) reserves.[8,9] In 2003, guidelines from the American Society of Anesthesiologists Task Force on the Management of the Difficult Airway included "face mask preoxygenation before initiating management of the difficult airway."[10] Because the "cannot intubate, cannot ventilate" situation is unpredictable, the need for preoxygenation is desirable in all patients.[8,11] In 2015, guidelines developed by Difficult Airway Society in the United Kingdom for the management of unanticipated difficult intubation included the statement that all patients should be preoxygenated before the induction of general anesthesia.[12]

Residual effects of anesthetics or inadequate reversal of muscle relaxants can complicate emergence from anesthesia. These effects can lead to decreased functional activity of the pharyngeal muscles, upper airway obstruction, inability to cough effectively, a 5-fold increase in the risk of aspiration, and attenuation of the hypoxic drive by the peripheral chemoreceptors.[13,14] Hypoventilation, hypoxemia, and loss of airway patency may follow these changes. Preoxygenation can also minimize neostigmine-induced cardiac arrhythmias.[15] In accordance, "routine" preoxygenation before the reversal of neuromuscular blockade and tracheal extubation has been recommended, given the potential for airway and ventilation problems.[16] Guidelines for the management of tracheal extubation proposed in 2012 by the Difficult Airway Society in the United Kingdom include the statement that it is vital to preoxygenate before

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extubation because of various perioperative anatomical and physiologic changes that may compromise gas exchange.[17] Preoxygenation has also been recommended before any interruption of ventilation, such as during open tracheobronchial suctioning.[16]

The current review describes the physiologic basis and clinical benefits of preoxygenation. Special considerations for preoxygenation in high-risk patient populations are discussed. Over the years, concerns have been expressed in the literature regarding potential undesirable effects of preoxygenation. These effects include delayed diagnosis of esophageal intubation, tendency to cause absorption atelectasis, production of reactive oxygen species, and adverse hemodynamic changes. We describe these effects and discuss whether they justify modifying preoxygenation in selected clinical situations.

PREOXYGENATION: PHYSIOLOGIC BASIS, EFFICACY, AND EFFICIENCY

Preoxygenation increases the body O_2 stores, the main increase occurring in the functional residual capacity. The size of the increases in O_2 volume in the various body tissues is difficult to assess with precision, but assuming that the partition coefficient for gases approximates the gas-water coefficients, the estimated increases are appreciable (Table 1; Figure 1).[18,19] The effectiveness of preoxygenation is assessed by its efficacy and efficiency.[8] Indices of efficacy include increases in the fraction of alveolar O_2 (F_{AO_2}),[20–22] decreases in the fraction of alveolar nitrogen (F_{AN_2}),[23,24] and increases in arterial O_2 tension (Pa_{O_2}).[25–27] Efficiency of preoxygenation is assessed from the decline of oxyhemoglobin desaturation (Sa_{O_2}) during apnea.[28–30]

Table 1. Body O_2 Stores (in mL) During Room Air and 100% O_2 Breathing

Body Store	Room Air	100 % O_2
Lungs	450	3000
Blood	850	950
Dissolved in tissue fluids	50	100
Combined with myoglobin	200	200
Total	1550	4250

Adapted from Nunn.[18]

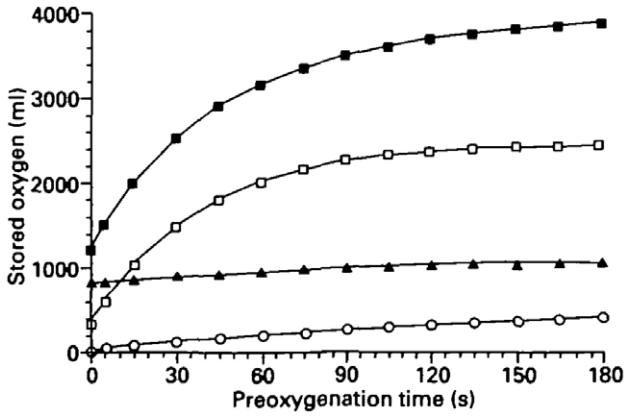

Figure 1. Variation in the volume of O_2 stored in the functional residual capacity (□), blood (▲), tissue (○), and whole body (■) with the duration of preoxygenation. Published with permission from Campbell and Beatty.[19]

Preoxygenation increases F_{AO_2} and decreases F_{AN_2} (Figure 2).[31] The key to achieving maximal preoxygenation is the washout of alveolar nitrogen (N_2). The terms preoxygenation and denitrogenation have been used synonymously to describe the same process. In a subject with normal lung function, the O_2 washin and the N_2 washout are exponential functions and are governed by the time constant (t) of the exponential curves. This constant is proportional to the ratio of alveolar ventilation to functional residual capacity. Because preoxygenation before anesthetic induction is typically performed using a semiclosed circle absorber circuit, the washout of the circuit must also be considered using the time constant of the circuit, which is the time required for flow through a container (volume) to equal its capacity. Thus, there are 2 stages of preoxygenation (Table 2),[16] the washout of the circuit by O_2 flow and the washout of the functional residual capacity by the alveolar ventilation. After 1 *t*, the O_2 in the functional residual capacity will be increased by 63%; after 2 *t*, by 86%; after 3 *t*, by 95%; after 4 *t*, by approximately 98%. The end points of maximal preoxygenation and denitrogenation have been defined as an end-tidal O_2 concentration (Et_{O_2}) of approximately 90% and an end-tidal N_2 concentration (Et_{N_2}) of 5%.[19,20] In an adult subject with a normal functional residual capacity and oxygen consumption (V_{O_2}), an $Et_{O_2} > 90\%$ implies that the lungs contain >2000 mL of O_2, which is 8 to 10 times the V_{O_2}.[8,32] Because of the obligatory presence of carbon dioxide (CO_2) and water vapor in the alveolar gas, an Et_{O_2} >94% cannot be easily achieved.

Many factors affect efficacy and efficiency (Table 3).[16] Factors affecting the efficacy of preoxygenation include the F_{IO_2}, duration of preoxygenation, and the alveolar ventilation/functional residual capacity ratio. Failure to achieve an F_{IO_2} near 1.0 can be caused by a leak under the face mask,[34,35] rebreathing of exhaled gases, and the use of resuscitation bags incapable of delivering high F_{IO_2}.[31]

Bearded patients, edentulous patients, elderly patients with sunken cheeks, use of the wrong size face mask, improper use of head straps, and the presence of gastric tubes are common factors causing air entrainment and a lower F_{IO_2}. The absence of a normal capnographic tracing, and a lower than expected end-tidal carbon dioxide concentration (Et_{CO_2}) and Et_{O_2} should alert the anesthesiologist to the presence of leaks in the anesthetic circuit.[8] F_{IO_2} can also be influenced by the duration of breathing, technique of breathing, and the level of the fresh gas flow (FGF).[36] Adequate time is needed to achieve maximal preoxygenation. With an F_{IO_2} near 1.0, most healthy adults with tidal volume breathing can reach the target level of an $Et_{O_2} >$ 90% within 3 to 5 minutes. The half-time for an exponential change in the fraction of F_{AO_2} following a step change in F_{IO_2} is given by the equation: $F_{AO_2} = 0.693 \times$ Volume of gas in the functional residual capacity / alveolar ventilation. With a functional residual capacity of 2.5 L, the half-times are 26 seconds when alveolar ventilation = 4 L/min and 13 seconds when alveolar ventilation = 8 L/min.[8] These findings indicate that hyperventilation can reduce the time required to increase the O_2 stores in the lungs, which provides the basis for using deep breathing as an alternative to tidal volume breathing.[27,37–39] A wide range of preoxygenation techniques have been described (Table 4).[16]

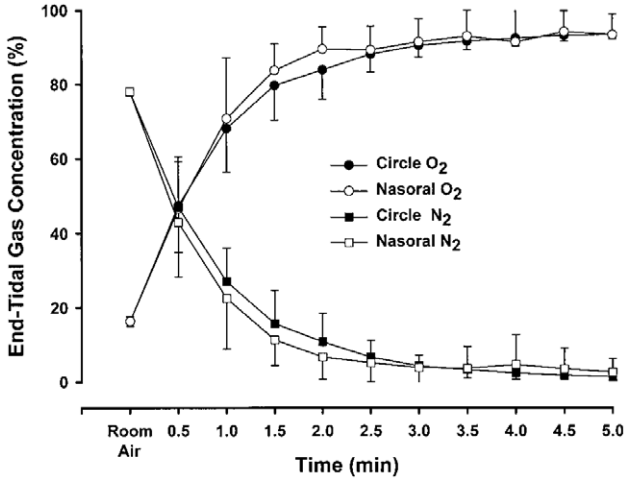

Figure 2. Comparison of mean end-tidal O_2 and N_2 concentration obtained at 30-second intervals during 5-minute period of spontaneous tidal volume oxygenation using the circle absorber and NasOral systems in 20 volunteers. Data are mean ± SD. Published with permission from Nimmagadda et al.[31]

Table 2. Stages of Preoxygenation

Stage	Description	Determinant of *t*	Recommendation
1	Washout of anesthesia circuit by O_2 flow	Size of circuit/O_2 flow rate	Washout of circuit by high O_2 flow before placing face mask
2	Washout of FRC by VA	FRC/VA	Use of O_2 flow rate that eliminates rebreathing

Abbreviations: FRC, functional residual capacity; t, time required for flow through a container (volume) to equal its capacity; VA, alveolar ventilation.
Adapted from Baraka and Salem.[16]

Table 3. Factors Affecting the Efficacy and Efficiency of Preoxygenation

- Efficacy
  - Inspired oxygen concentration
    - Presence of leak
    - Anesthetic system used
    - Level of FGF
    - Type of breathing (tidal volume or deep breathing)
  - Duration of breathing
  - VA/FRC ratio
- Efficiency
  - Oxygen volume in lungs
    - Alveolar oxygen tension
    - FRC
  - Systemic oxygen supply versus demand balance
    - Arterial oxygen content
    - Cardiac output
    - Whole body oxygen consumption

Abbreviations: FGF, fresh gas flow; FRC, functional residual capacity; VA, alveolar ventilation.
Adapted from Baraka and Salem.[16]

Increasing the FGF from 5 to 10 L does not increase appreciably the F_{IO_2} during tidal volume breathing, although it does so during deep breathing.[36] Because of the breathing characteristics of the circle system, the minute ventilation during deep breathing may exceed the FGF, resulting in rebreathing of N_2 in the exhaled gases, consequently decreasing the F_{IO_2}. However, during tidal volume breathing, rebreathing of N_2 in the exhaled gases is negligible and thus increasing the FGF from 5 to 10 L has minimal effect on F_{IO_2}.[36] Regardless of the technique used, the goal is to reach the end point of maximal preoxygenation, which can be easily measured with most anesthesia monitors.

All investigations have demonstrated that preoxygenation markedly delays arterial oxyhemoglobin desaturation during apnea.[8,21,23,28] The extent of this delay in desaturation depends on the efficacy of preoxygenation, the capacity for O_2 loading, and the V_{O_2}.[33] Patients with a decreased capacity for O_2 transport (decreased functional residual capacity, P_{AO_2}, arterial O_2 content, or cardiac output) or those with an increased V_{O_2} develop oxyhemoglobin desaturation more rapidly during apnea than healthy patients.[8,28] Farmery and Roe[40] developed and validated a computer model describing the rate of oxyhemoglobin desaturation during apnea. The model is particularly useful for analyzing oxyhemoglobin desaturation values below 90%. These values are dangerous to allow in human subjects, because below 90%, there will be a steep decline of P_{AO_2} because of the sigmoid shape of oxyhemoglobin dissociation curve. In a healthy 70-kg patient, when F_{AO_2} is progressively decreased from 0.87 (F_{IO_2} of 1.0) to 0.13 (air), the apnea time to 60% S_{AO_2} is decreased from 9.9 to 2.8 minutes (Figure 3).[28]

PREOXYGENATION FOR HIGH-RISK PATIENT POPULATIONS

Pregnant Patients

Rapid sequence induction/intubation is commonly performed in pregnant women who are given general anesthesia and preoxygenation is essential in these patients. Maximal preoxygenation can be achieved more rapidly in pregnant than in nonpregnant women because of a higher alveolar ventilation and a lower functional residual capacity.[22,41] However, during apnea, pregnant women tend to develop oxyhemoglobin desaturation more rapidly because of a limited O_2 volume in their smaller functional residual capacity combined with an increased V_{O_2}. The time required for S_{AO_2} to decrease to 95% during apnea was found to be 173 seconds in pregnant women and 243 seconds in nonpregnant women in the supine position.[42] Use of the 45° head-up position results in an increase in desaturation time in nonpregnant women but not in pregnant women. It is possible that the gravid uterus prevents the descent of the diaphragm and does not allow the expected increase in functional residual capacity in the head-up position.[42] In pregnant women, the 4 deep breathing technique is inferior to the 3-minute tidal volume breaths technique and should not be used, except in emergencies.[43] An increased minute ventilation in pregnant women requires that an O_2 flow of 10 L/min be used during preoxygenation.[44]

Morbidly Obese Patients

Studies have demonstrated that, following preoxygenation with tidal volume breathing for 3 minutes, the time required for S_{AO_2} to fall to 90% during apnea is markedly reduced in morbidly obese patients (BMI > 40 kg/m^2) compared with nonobese patients.[45,46] During apnea following preoxygenation, the average time to reach an S_{AO_2} of 90% in patients

with normal body weight was 6 minutes, whereas that in morbidly obese patients was only 2.7 minutes.[47] These findings are particularly concerning because morbid obesity is often complicated by obstructive sleep apnea, which can make mask ventilation and intubation more difficult. Rapid oxyhemoglobin desaturation during apnea in morbidly obese patients was attributed to an increased Vo_2 and a markedly reduced functional residual capacity. The supine position enhances this decrease in functional residual capacity because of a cephalad displacement of the diaphragm. Placing severely obese patients in the 25° head-up position during preoxygenation has been shown to prolong the time of desaturation by approximately 50 seconds.[48]

Some anesthesiologists may prefer awake fiberoptic intubation rather than rapid sequence induction/intubation in morbidly and super morbidly obese patients (BMI > 50 kg/m^2), especially when they have associated problems.[49] An advantage of this approach is the maintenance of airway patency during spontaneous breathing until an "unhurried" tracheal intubation can be accomplished. Face mask preoxygenation should precede intubation attempts and should be continued with the placement of a nasal cannula or an O_2 catheter in the oropharynx. O_2 flow (up to 5 L/min) through the working channel of the scope has the double advantage of insufflating O_2 and enhancing laryngeal visualization by preventing fogging and pushing secretions away. It is important to recognize that airway obstruction can hinder the egress of gases from the fiber-optic scope, which, if prolonged, can result in barotrauma. Thus, caution cannot be overemphasized when this approach is utilized. Techniques to enhance preoxygenation, which are described later, are especially important in morbidly and supermorbidly obese patients.

Table 4. Techniques of Preoxygenation

Tidal volume breathing
One vital capacity breath followed by tidal volume breathing
Single tidal capacity breath
Four deep breaths (4 inspiratory capacity breaths)
Eight deep breaths (8 inspiratory capacity breaths)
Extended deep breathing (12–16 inspiratory capacity breaths)

Adapted from Baraka and Salem.[16]

Pediatric Patients

Studies have demonstrated that maximal preoxygenation (Eto_2 = 90%) can be accomplished in children faster than in adults.[50,51] With tidal volume breathing, an Eto_2 of 90% can be reached within 100 seconds in almost all children, whereas with deep breathing, it can be reached in 30 seconds.[50,51] Nevertheless, because children have a smaller functional residual capacity and a higher Vo_2 than adults, they are at a greater risk for developing hypoxemia, when there is interruption in O_2 delivery, such as during apnea or airway obstruction.[52–54] In a comparison of 3 groups of children who breathed O_2 (Flo_2 = 1.0) with tidal volume breathing for 1, 2, and 3 minutes before apnea, the time needed for Sao_2 to decrease from 100% to 95% and then to 90% during apnea was least in those who breathed O_2 for 1 minute and there was no difference between those who breathed O_2 for 2 and 3 minutes.[55] Based on these findings, 2 minutes of preoxygenation with tidal volume breathing seems sufficient for a maximum benefit and to allow a safe period of apnea.[55] The benefit of preoxygenation is greater in an older child than that in an infant. For example, in an 8-year-old child, the duration of safe period of apnea can be extended from 0.47 minute without preoxygenation to 5 minutes or longer with preoxygenation.[56] The younger the child, the faster the onset of desaturation.[53,54,57] Most infants reach a Sao_2 of 90% in 70 to 90 seconds after the onset of apnea (in spite of preoxygenation),[58] and this period can be even shorter in the presence of upper respiratory tract infection.[59] Pediatric anesthesiologists have expressed concerns

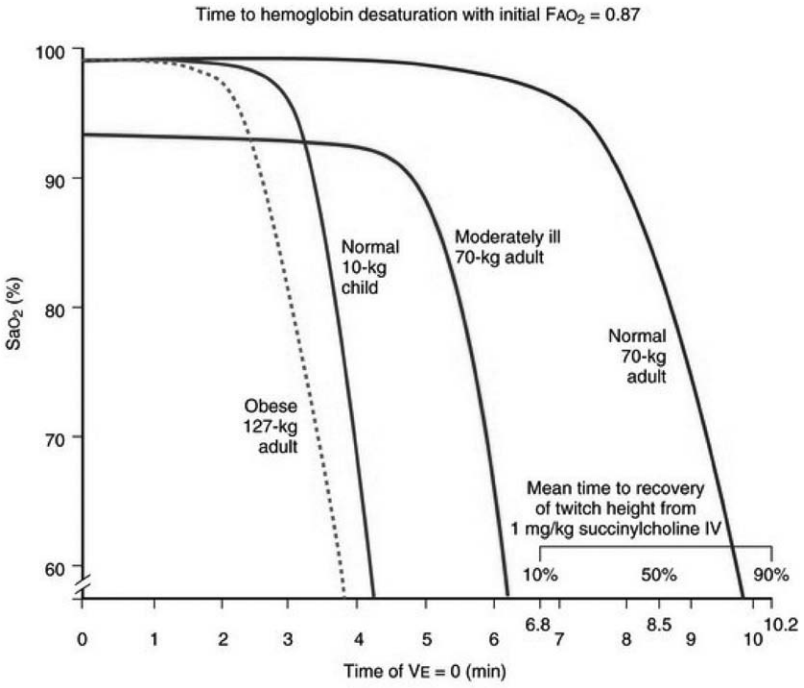

Figure 3. Arterial oxyhemoglobin saturation (Sao_2) versus time of apnea in an obese adult, a 10-kg child with low functional residual capacity and high ventilation, and a moderately ill adult compared with a healthy adult. F_{AO_2} indicates fractional alveolar oxygen concentration; VE, expired volume. Published with permission from Benumof et al.[28]

about the use of the "adult" version of the rapid sequence induction/intubation technique in children.[60] The concerns include the safe duration of apnea and the potential for cricoid pressure-induced airway obstruction. A modified version of the rapid sequence induction/intubation technique, with emphasis on complete muscular relaxation, gentle manual ventilation using high O_2 concentration without cricoid pressure and sufficient anesthetic depth before intubation would seem more appropriate in children.[61]

Elderly Patients

Aging is associated with significant structural and physiologic changes in the respiratory system.[62,63] The changes include weakened respiratory muscles and parenchymal alterations within the lungs accompanied by a decrease in the elastic recoil. Lung volumes are decreased with increased closing volume, resulting in ventilation—perfusion mismatch, a reduced pulmonary reserve, and an impaired O_2 uptake at the lung. Even though basal Vo_2 decreases with aging, the impaired O_2 uptake produces a more rapid desaturation during apnea under anesthesia.[63] In elderly patients, tidal volume breathing for 3 minutes or longer has been shown to be more effective than the 4 deep breathing technique.[64,65]

Patients With Pulmonary Disease

Both efficacy and efficiency can be adversely affected by pulmonary disease. Significant pulmonary disease is associated with a decreased functional residual capacity, appreciable ventilation—perfusion mismatch, and an increased Vo_2, which can reduce the margin of safety. Anesthesia has been shown to cause further impairment to gas exchange in patients with chronic obstructive pulmonary disease.[66] Even brief interruption of ventilation, such as during suctioning can result in significant desaturation. However, atelectasis is not a consequence, possibly because chronic hyperinflation of the lungs resists volume decrease and collapse.[67] Maximal preoxygenation, which is essential in these patients, may require as much as 5 minutes or longer with tidal volume breathing.[68]

Patients at High Altitude

High altitude does not alter the concentration of inspired O_2 (21%), but the reduced barometric pressure produces a decrease in the partial pressure of alveolar and arterial Po_2.[69] For example, in Flagstaff, AZ, with an altitude of 2100 m (approximately 7000 feet above sea level), Pao_2 is reduced from the normal value of 100 mm Hg to approximately 74 mm Hg.[69] As altitude increases, Pao_2 decreases exponentially. No studies, to our knowledge, have been performed to assess the effect of high altitude on preoxygenation. This is difficult to predict because of the multiple determinants of preoxygenation and the potential influence of compensatory mechanisms, especially in acclimatized individuals. It is possible that patients at high altitude will require a longer duration of preoxygenation to achieve an acceptable degree of protection, but this remains to be confirmed experimentally.

TECHNIQUE OF PREOXYGENATION

To provide effective preoxygenation, a methodical approach is necessary. The importance of preoxygenation with a tight-fitting mask should be explained to the patient beforehand. Once preoxygenation is initiated, Eto_2 and Fio_2 values should be monitored closely. If the Eto_2 value does not increase as expected, the anesthesia provider may have to hold the mask with both hands and/or replace the mask with a better-fitting one. Whenever possible, the induction should not start until the Eto_2 value approximates or exceeds 90%.

TECHNIQUES TO ENHANCE PREOXYGENATION

Apneic Diffusion Oxygenation

Preoxygenation followed by "apneic diffusion oxygenation" is an effective maneuver for prolonging the safe duration of apnea.[16,70–73] The physiologic basis of this maneuver is as follows. During apnea in adults, Vo_2 averages 230 mL/min, whereas CO_2 delivery to the alveoli is only 21 mL/min.[16] The remaining 90% (or more) of CO_2 is buffered within body tissues. The result is that lung volume decreases initially by 209 mL/min, which creates a pressure gradient between the upper airway and the alveoli, and provided that the airway is not obstructed, O_2 enters the lung via diffusion. Because CO_2 cannot be exhaled, $Paco_2$ rises from 8 to 16 mm Hg in the first minute of apnea, followed by a linear rise of approximately 3 mm Hg/min.[74]

The benefit of apneic diffusion oxygenation is dependent on achieving maximal preoxygenation before apnea, maintaining airway patency, and the existence of a high functional residual capacity to body weight ratio. Fraioli et al[75] demonstrated that patients with a low predicted functional residual capacity/body weight ratio (37 ± 9 mL/kg) could not tolerate apneic oxygenation for more than 5 minutes, whereas patients with a high predicted functional residual capacity/body weight ratio (53 ± 8 mL/kg) could tolerate apneic oxygenation for at least 15 minutes. Although Pao_2 falls in direct relation to PAo_2, Sao_2 remains greater than 90% as long as the hemoglobin can be reoxygenated in the lungs.[32,71,75] Sao_2 starts to decrease only after the O_2 stores in the lungs are depleted, and Pao_2 falls below 60 mm Hg. When Sao_2 is <80%, the rate of decrease in saturation is approximately 30%/min. In the presence of an airway obstruction, gas volume in the lungs decreases rapidly, and intrathoracic pressure decreases at a rate dependent on lung compliance and Vo_2. When the airway obstruction is relieved, a rapid flow of O_2 into the lungs resumes, and with high Fio_2, preoxygenation is restored.[32] Some studies have demonstrated that, with a patent airway, apneic diffusion oxygenation can maintain Sao_2 above 90% for up to 100 minutes.[71] When Fio_2 is at a high level, a small increment can produce a profoundly disproportionate delay in hemoglobin desaturation; the delay in hemoglobin desaturation achieved by increasing Fio_2 from 0.9 to 1.0 was greater than that achieved by increasing Fio_2 from 0.21 to 0.9 (Figure 4).[76]

Apneic diffusion oxygenation can be achieved by maximal face mask preoxygenation followed by O_2 insufflation up to 15 L/min through a nasopharyngeal or an oropharyngeal cannula or through a needle inserted in the cricothyroid membrane. In healthy patients with an unobstructed airway, this technique can provide at least 10 minutes of adequate oxygenation. The clinical applications include patients who are difficult to intubate or ventilate and

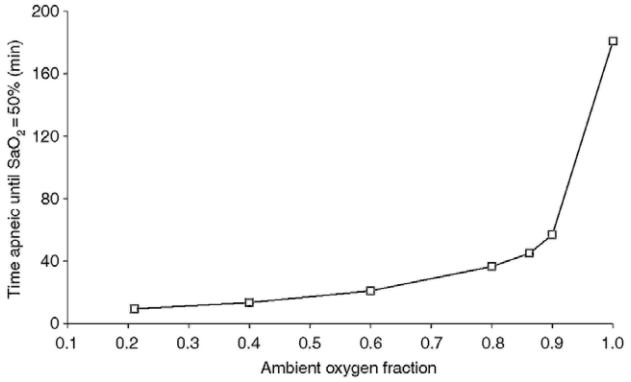

Figure 4. The time (duration of apnea) required to reach 50% Sao_2 with an open airway exposed to various ambient O_2 fractions. Published with permission from McNamara and Hardman.[76]

patients with limited oxygen reserves. The technique can also be used during bronchoscopy and can provide adequate time for short glottic surgical procedures unimpeded by the presence of a tracheal tube or the patient's respiratory excursions. Although oxygenation can be maintained for longer periods, a limiting factor of apneic oxygenation is the progressive rise of $Paco_2$ during apnea.[74]

Continuous Positive Airway Pressure and Positive End-Expiratory Pressure

Use of continuous positive airway pressure (CPAP) during preoxygenation of obese patients did not delay the onset of desaturation, because the functional residual capacity returned to the pre-CPAP level when the patient was induced and the mask was removed.[78] However, the use of CPAP during preoxygenation followed by mechanical ventilation using positive end-expiratory pressure (PEEP) for 5 minutes before removing the mask and securing the airway, delayed the desaturation time.[78,79]

Noninvasive Bilevel Positive Airway Pressure

BiPAP (bilevel positive airway pressure; inspiratory positive airway pressure and expiratory positive airway pressure) combines the benefits of pressure support ventilation and CPAP and keeps the lungs open during the entire respiratory cycle. BiPAP has been used during preoxygenation to decrease intrapulmonary shunting and to increase the margin of safety during apnea in morbidly obese patients.[80] The technique has also been used to reduce postoperative pulmonary dysfunction and to treat patients with respiratory failure from various etiologies.[81]

Transnasal Humidified Rapid Insufflation Ventilatory Exchange

Transnasal humidified rapid insufflation ventilatory exchange (THRIVE) is a new technique that is available for use in critically ill patients and in patients with difficult airways. The technique combines the benefits of apneic oxygenation and CPAP with a reduction in CO_2 levels through gaseous mixing and flushing of the dead space (Figure 5).[82] THRIVE is administered through a standard, commercially available, nasal, high-flow oxygen delivery system. Insufflation of O_2 up to 70 L/min via a purpose-made nasal cannula is used initially to provide preoxygenation, which can be continued during intravenous induction and neuromuscular blockade until a definitive airway is secured. CPAP of approximately 7 cm H_2O splints the upper airways and reduces shunting.[84] The THRIVE technique has been demonstrated to appreciably prolong the safe duration of apnea while avoiding increase in CO_2.[83]

POTENTIAL RISKS OF PREOXYGENATION

Delayed Diagnosis of Esophageal Intubation

Although an unrecognized esophageal intubation ultimately results in severe hypoxemia, minutes may elapse before this occurs. Preoxygenation extends the time period before hypoxemia ensues and, thus, delays the detection of a misplaced endotracheal tube when Spo_2 is being used as an indicator. Cases attributing a delayed diagnosis of esophageal intubation to preoxygenation[85,86] prompted some clinicians to suggest abandoning the maneuver.[84] However, this would seem to be an extreme reaction when the practice has proven benefits. Furthermore, it should be emphasized (1) that normal pulse oximetry readings after intubation should not be regarded as evidence of proper endotracheal tube placement and (2) that a severe fall in Spo_2 is a relatively late manifestation of an esophageal intubation. In spite of occasional false-positive and false-negative results, identification of CO_2 in the exhaled gas (end-tidal CO_2), which is readily available on all anesthesia monitors, is a well-accepted and routinely used indicator of proper endotracheal tube placement. The reader is referred to airway management texts and review articles discussing the methods of verification of endotracheal tube placement.[87]

Absorption Atelectasis

Atelectasis occurs in 75% to 90% of healthy individuals undergoing general anesthesia,[87,88] and absorption atelectasis is the most common side effect of preoxygenation. It is initiated by 2 mechanisms during anesthesia.[89–92] One mechanism is the decrease in the functional residual capacity. Both the supine position and induction of anesthesia reduce lung volume, so that it approximates the residual volume. The end-expiratory volume may be lower than the closing capacity leading to airway closure and collapse of the dependent areas of the lung. The second mechanism is compression atelectasis. This is because of changes in the shape of the chest wall, spine, and diaphragm, which cause an increase in intraabdominal pressure leading to compression of the thoracic cavity and airway closure. Normally, O_2 shares alveolar space with other gases, principally N_2 which is poorly soluble in plasma and therefore remains in high concentration in alveolar gas. In the presence of a partial or complete airway closure, the gases gradually diffuse out of the alveoli and are not replaced. During air breathing, emptying of the lung is limited by the sluggish diffusion of N_2. However, during preoxygenation, the rapid replacement of N_2 with O_2 promotes loss of gas from the lung to the blood stream resulting in alveolar collapse, that is, absorption atelectasis. Absorption of gas does not in itself cause atelectasis, but in effect accelerates collapse should airway closure occur from either of the above 2 mechanisms.[91,92]

Techniques that have been proposed to decrease the extent of absorption atelectasis following preoxygenation

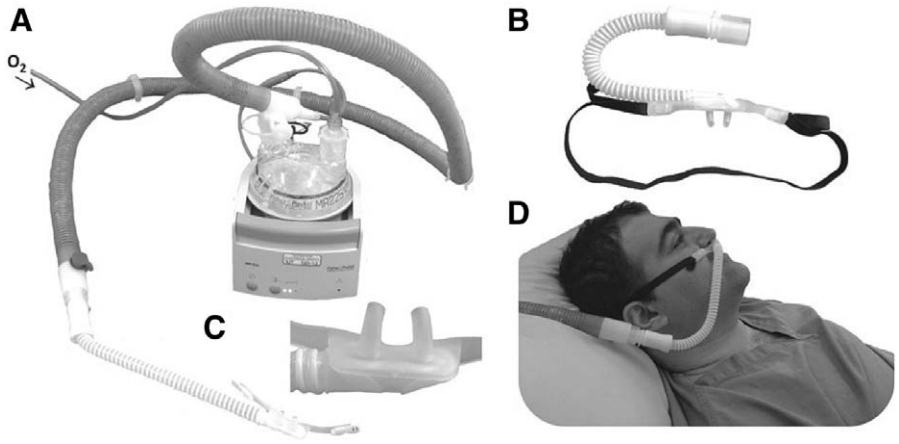

Figure 5. The OptiFlow high-flow humidified O_2 delivery system. The O_2 humidification unit (A) received O_2 from a standard O_2 regulator and delivers humidified O_2 to a custom-built transnasal O_2 cannula (B and C) like a standard nasal O_2 cannula (D). Published with permission from Patel and Nouraei.[82]

Table 5. Effect of F_{IO_2} Before Induction of Anesthesia on Time for Sao_2 to Reach 90%, Along With the Associated Atelectasis

F_{IO_2} Before Induction	Time (s) to Sao_2 = 90%	% Atelectasis
0.6	213 (69)	0.3 (0.3)
0.8	303 (59)	1.3 (1.2)
1.0	411 (84)	5.6 (3.4)

Data are mean (SE).
Abbreviations: F_{IO_2}, fraction of inspired oxygen; Sao_2, arterial oxyhemoglobin saturation.
Adapted from Edmark et al.[95]

are (1) decreasing the concentration of F_{IO_2} and (2) various recruitment maneuvers. Studies using computer modeling, as well as those involving actual measurements in patients using computerized tomography (CT), have demonstrated that decreasing the value of F_{IO_2} can have a profound effect on the extent of atelectasis.[93–96] Computer model of absorption atelectasis predicted that preoxygenation with an F_{IO_2} of 1.0 would accelerate the collapse of the lung.[93] A CT study found that atelectasis was less when patients were ventilated with 30% O_2 during induction of anesthesia than when 100% O_2 was used.[94] Another CT study evaluated the effect of stepwise variations in inspired O_2 on the extent of atelectasis and the time to arterial desaturation (Table 5).[95] The investigators found (1) that atelectasis was significant in patients receiving 100% O_2, but that it was small and virtually absent in patients receiving 80% and 60% O_2, respectively and (2) that the time to desaturation fell with decreasing O_2 concentration. Studies have also shown that administering 100% O_2 during emergence from anesthesia can increase atelectasis. Benoit et al[96] found a 6.8% atelectasis in patients awakened on an F_{IO_2} of 1.0 compared with 2.6% in those awakened on an F_{IO_2} of 0.4.

Recruitment maneuvers are commonly performed in patients under general anesthesia, but they have particular value in conjunction with preoxygenation. These maneuvers include CPAP, PEEP, and/or reexpansion maneuver. A CT study found that the combined use of CPAP (6 cm H_2O) during 5 minutes of preoxygenation with face mask while breathing spontaneously, and PEEP (6 cm H_2O) during mask ventilation for additional 5 minutes during induction of anesthesia, prevented the marked increase in atelectasis that was evident in a control group.[77] A reexpansion maneuver is a vital capacity maneuver. Rothen et al[97] evaluated the dynamics of reexpansion of atelectasis with a vital capacity maneuver during general anesthesia. They found that reopening of the alveoli occurred mainly during the first 7 to 8 seconds of application of an airway pressure of 40 cm H_2O. Typically, this maneuver is used soon after tracheal intubation and before tracheal extubation.

Production of Reactive Oxygen Species

Oxygen is a paramagnetic atom containing 2 unpaired electrons in its outer shell that usually exists in the form of dioxygen (O_2). In biological tissues, the dioxygen molecule can be accidentally or deliberately split, producing reactive oxygen species, which include superoxide anion, hydroxyl radical, and hydrogen peroxide.[98–100] Reactive oxygen species can react with critical molecular components, such as lipids, DNA, and proteins, causing significant cellular damage.[101,102] Although endogenous antioxidant mechanisms are normally sufficient to prevent high tissue concentrations of reactive oxygen species, these mechanisms can become overwhelmed resulting in oxidative stress.[102,103] It is known that prolonged use of F_{IO_2} = 1.0 can cause production of reactive oxygen species. Clinical manifestations are pulmonary edema, acute respiratory distress syndrome, retinal detachment, retinopathy of prematurity, and seizures.[104] The signs of early lung injury begin to appear after 12 hours of high concentrations of O_2 breathing.[105] Thus, because of its short duration, cellular injury due to reactive oxygen species would not be applicable to preoxygenation.

Cardiovascular Responses

The cardiovascular responses during preoxygenation have received limited attention and have not been well characterized. But there have been many studies, both in humans and animal models, assessing the steady state cardiovascular responses during high O_2 breathing, which may provide insight into the hemodynamic changes during preoxygenation. However, the changes in Pao_2 during preoxygenation are dynamic and brief, and, furthermore, they have been demonstrated to vary in different patient populations. Thus, caution should be exercised in extrapolating the experimental findings described below to a given patient undergoing preoxygenation.

Several studies in normal male subjects have demonstrated that breathing 100% O_2 causes a modest decrease

in heart rate accompanied by a parallel decrease in cardiac output. Systemic vascular resistance and arterial blood pressure increase.[106–108] These changes are attributable to a reflex loop, either chemoreceptor or baroreceptor in origin. Since atropine abolishes the reduction in heart rate, this response is mediated by the vagus nerves.[107]

A number of physiologic studies have assessed the effect of inhalation of 100% O_2 in the human coronary circulation.[109–113] Hyperoxia consistently caused a marked decrease in coronary blood flow (reflecting coronary vasoconstriction) accompanied by a decrease in myocardial oxygen consumption. The direct coronary vasoconstrictor effect of hyperoxia is due to the oxidative inactivation of nitric oxide[110,112] and other vasodilators released from the vascular endothelium and to closure of the ATP-sensitive K^+ channels.[113,114] Investigations in patients with normal coronary arteries have indicated that, despite the decrease in coronary blood flow, oxygenation at the level of the myocytes remains adequate, as indicated by continued myocardial lactate extraction rather than conversion to production.[108,109] This is likely explained by the ability of the increase in arterial O_2 content to blunt the reduction in coronary O_2 supply caused by the reduced coronary blood flow combined with a reduction in myocardial O_2 demand, secondary to the hyperoxia-induced bradycardia. Metabolic findings in patients with severe coronary artery disease have been inconsistent. Some studies have found that O_2 breathing by these patients converts myocardial lactate production to extraction, suggesting a beneficial effect,[108] whereas others have found that O_2 breathing precipitates or accentuates myocardial lactate production, implying ischemic changes.[110]

It is well established that inhalation of high O_2 can also reduce cerebral blood flow because of vasoconstriction.[115–118] It has been proposed that this effect may be because, at least in part, of the associated decrease in $Paco_2$ that accompanies high O_2 breathing rather than to a direct effect of O_2.[116] The mechanism for the decrease in $Paco_2$ is as follows. When Pao_2 is increased by inhalation of 100% O_2, the CO_2 dissociation curve for blood is altered (the Christiansen-Douglas-Haldane effect), such that there is a reduction in the affinity of blood for CO_2. This produces an increase in cerebral tissue Pco_2 and hydrogen ion concentration, which stimulates respiration with a result that $Paco_2$ decreases causing cerebral vasoconstriction.[117,118] Investigators have also assessed the effect of hyperoxia on cerebral O_2 consumption, using a functional magnetic resonance technique.[117] They found that hyperoxia causes an approximate 20% decrease in cerebral O_2 consumption, reflecting reduced neural activity.[117] It was speculated that the decrease in cerebral O_2 consumption was because of the ability of reactive oxygen species to damage lipids and proteins, and, in turn, decrease the enzyme activity in oxidative metabolic pathways.

Studies in animal models have demonstrated that hyperoxia causes vasoconstriction and a decrease in blood flow in peripheral vascular beds, including the kidney, gastrointestinal tract, and hindlimb.[115,119,120] Whether this vasoconstriction is because of a direct effect of O_2 on vascular smooth muscle or reflex-mediated via an arterial chemoreceptor/autonomic nerve remains unclear. Regardless, it is doubtful that changes in the peripheral vascular beds would have any important clinical effect during preoxygenation. The cardiovascular findings to date provide no justification for limiting the use of preoxygenation.

CONCLUSIONS

The literature provides overwhelming evidence that preoxygenation, whether instituted before induction or to emergence from anesthesia, delays the onset of hypoxemia during apnea. On that basis, preoxygenation should be performed in all patients given general anesthesia. Preoxygenation should also be performed whenever there is an anticipated interruption of O_2 delivery, such as during open tracheobronchial suctioning, and before and during awake fiberoptic intubation, especially in high-risk patients, such as the supermorbidly obese. The technique should be performed correctly, with monitoring of Eto_2. Because the advantage of preoxygenation may be blunted in high-risk patients, various maneuvers are available to prolong its effectiveness. The clinician should be familiar with these maneuvers. Absorption atelectasis during preoxygenation can be readily minimized, and thus it should not be a deterrent to the routine use of the technique. ■

DISCLOSURE

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